By way of this amendment, claims **2, 18, and 34** have been rewritten.

Upon entry of this amendment, claims **2-16, 18-30, and 34-48** will be pending.

Summary of the Amendment

Claims 2, 18, and 34 have been amended to incorporate the subject matter of claims from which they previously depended. No new matter has been added.

Discussion of the Present Invention

The present invention provides methods of inhibiting osteoclastogenesis, methods of treating diseases characterized by bone loss, and methods of inhibiting bone resorption. The methods generally comprise administering to a patient an amount of a TRANCE/RANK inhibitor effective to inhibit the disease or disorder. The TRANCE/RANK inhibitor is designed from a binding loop of a TNF-R superfamily member. In some preferred embodiments, the TRANCE/RANK inhibitor is a peptide which corresponds in primary sequence to a binding loop of TNF-R-p55.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-48 were rejected under 35 U.S.C. §112, first paragraph. The Office Action alleged that the specification, "while being enabling for treatment in vitro using the WP9QY peptide, does not reasonably provide enablement for treatments using other peptides or for in vivo treatments in patients." (Office Action at page 2). Applicants traverse this rejection.

The Office Action alleges that even in the claims which "require SEQ ID NOS: 12-15 to function as the inhibitors . . . there is, however, only a single working example showing the effect of an inhibitor to achieve the goal of inhibition of osteoclastogenesis, which is SEQ ID NO: 13, WP9QY." (Office Action at pages 2-3). The Office Action also alleges that although "the level of skill in the art is high, it is extremely unpredictable which alterations in the peptide sequence of WP9QY or what other sequences would function to inhibit osteoclastogenesis and would function to treat, in patients, bone loss or inhibit bone resorption" and refers to a citation from the Yamaguchi *et al.* reference (J. Biol. Chem, 273(9):5117-5123, 1998) which states that "the biological activity of the mutants was not

accurately determined in their study." (Office Action at page 3).

Applicants respectfully point out that the Examiner has misconstrued the Yamaguchi reference. Applicants note that the Examiner has read the quotation in isolation without taking into account the language preceding the quotation. The complete quotation is as follows:

> Recently, Simonet et al have reported the isolation of a cDNA coding for osteoprotegrin, a protein identical to OCIF. They showed that the first four domains alone can exert its inhibitory activity *in vitro* by analyzing the biological activity of C-terminal truncation mutants. However, the biological activity of the mutants was not accurately determined in their study. We first found that conditioned medium of cells producing ΔD567 was capable of inhibiting osteoclastogenesis in a dose-dependent manner (data not shown). Then, the mutant was purified to homogeneity to determine the potency. By analyzing the *in vitro* biological activity of the mutant, we concluded that the N-terminal portion of OCIF is sufficient to inhibit osteoclastogenesis, although the potency is approximately one-tenth that of wild-type OCIF.

(Yamaguchi at pages 5122-5123; internal citations omitted; emphasis added).

The language referring to a failure to determine biological activity of the first four domains of OCIF refers to a study performed in the Simonet reference. The Yamaguchi reference fails to say that the prediction of which mutants were active was not possible or was difficult. Yamaguchi merely points out that the Simonet study did not **accurately** determine biological activity. Moreover, Yamaguchi points out that in their study (the Yamaguchi study), biological activity **was** determined and that the medium **did** inhibit osteoclastogenesis in a dose-dependent manner.

The Examiner also asserts that Yamaguchi supports unpredictability because Yamaguchi identified "alterations which function to inhibit osteoclastogenesis since a previous study [Simonet] found a loss of activity by mutants of OCIF." As set forth above, "Simonet did not **accurately** determine biological activity". The Examiner has failed to identify any element in Yamaguchi showing unpredictability of biological activity of potential inhibitors. Therefore, the art cited by the Examiner does **not** indicate that it is "unpredictable which alterations in the peptide sequence of WP9QY or what other sequences would function

to treat, in patients, bone loss or inhibit bone resorption."

Applicants respectfully submit that the specification as filed enables those of ordinary skill in the art to practice the full scope of the subject matter defined by the claims without undue experimentation. The enablement requirement is met if the specification enables the skilled artisan to determine, without undue experimentation, which species encompassed by a generic claim are effective for their intended purpose. *In re Angstadt*, 537 F.2d 498 (C.C.P.A. 1976). Section 112, first paragraph, does not require the specification to demonstrate the operativeness of every species encompassed by a generic claim. *Id.* In *Angstadt* the claimed invention involved a method of catalytically oxidizing hydrocarbons to form hydroperoxides. Appellants' specification disclosed numerous working examples, one of which described a catalytic oxidation reaction that yielded no hydroperoxides. Appellants also expressly stated in the specification that some of the catalysts encompassed by the claims yielded no hydroperoxides. In affirming the Examiner's rejection for lack of enablement, the Board stated that

> the specification states that not all of the complexes will produce hydroperoxides and neither discloses which of the complexes will not work nor gives any information as to how the operative catalysts might be determined, without undue experimentation. We believe that the specification leaves too much conjecture, speculation and experimentation and is insufficient in law to support the present claims containing the disputed language.

Id. at 501.

In reversing the Board's decision, the Court of Customs and Patent Appeals stated the following.

> If one skilled in this art wished to make and use a transition metal salt other than those disclosed in appellants' 40 runs, he would merely read appellants' specification for direction how to make and use the catalyst complex to oxidize the alkylaromatic hydrocarbons, and could then determine whether hydroperoxides are, in fact, formed...Since appellants have supplied the list of catalysts and have taught how to make and how to use them, we believe that the experimentation required to determine which catalysts will produce hydroperoxides would not be undue and

> certainly would not 'require ingenuity beyond that to be expected of one of ordinary skill in the art.'

Id. at 503 (citations omitted). The Court also stated that §112, first paragraph does not require disclosure of test data for **every** species covered by a claim because such a requirement would necessitate patent applications with thousands of examples and "would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments." *Id.* at 502. This is supported by the Court's decision in *In re Bundy*, stating that:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public.

In re Bundy, 209 U.S.P.Q. 48 (C.C.P.A. 1981).

The dissenting opinion in *Angstadt* contended that the specification was not enabling, but the majority dismissed the dissent's assertion by stating that:

> [t]he kind of 'guidance' which the dissent seems to contemplate is unrealistic in view of the nature of the invention. The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record...What the dissent seems to be obsessed with is the thought of catalysts which won't work to produce the intended result...Without undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them. The dissent wants appellants to make everything predictable in advance, which is impracticable and unreasonable.

Id. at 504. The Court concluded by holding that the evidence as a whole, including both the inoperative and operative examples, negated the PTO position that persons of ordinary skill in the art, given its unpredictability, would have to engage in undue experimentation to determine which catalysts would work for their intended purpose. *Id.*

Applicants respectfully submit that the present specification enables the skilled artisan to practice the full scope of the subject matter defined by the claims without undue

experimentation. Applicants are **not** required to provide a specification that demonstrates the operability of each and every inhibitor encompassed by the present claims. *In re Angstadt*, 537 F.2d at 504. Such a requirement is not only contrary to established precedent, but is also impracticable and unreasonable. *Id.*

The Office Action has acknowledged that the specification is enabling for treatment *in vitro* using the WP9QY peptide. If the skilled artisan wished to make and use inhibitors other than the WP9QY peptide, he or she need only review the specification and follow the abundant teachings provided regarding how to make and use ***any*** inhibitor encompassed by the claims. The experimentation required to determine which inhibitors are effective would not be undue and would not require ingenuity beyond that expected of one of ordinary skill in the art. As set forth in *In re Wands*, 858 F.2d 731, 737; 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-504; 190 USPQ 214, 217-19 (CCPA 1976):

> The test [for quantity of experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

The testing described in the present application is routinely carried out by those skilled in the art and is in no way "undue".

The Office Action also alleges that different test systems yield different results which are unpredictable. Further, the Office Action alleges that Applicants "without any evidence of efficacy . . . would purport to apply the results of an in vitro system which has only one functional inhibitor to human therapeutics." (Office Action at page 4).

For many years pharmaceutical researchers have used many different models to mimic higher animal systems. The purpose of these models is to predict which candidate compounds might be useful in the higher animal system. Model systems include *in vitro* assays and *in vivo* assays. Traditionally, pharmaceutical researchers start study of candidate compounds using *in vitro* assays and a relatively large number of candidate compounds. Compounds that show promise in *in vitro* models are then tested using lower animal *in vivo* models. Generally, the first *in vivo* model used to assess candidate compounds is a rodent,

typically mouse or rat. Ultimately, compounds which show sufficient activity in lower animal *in vivo* assays are tested in humans.

It is fundamental to this approach to drug discovery and development that only compounds that show promising activity in successive model assays are further tested. Compounds that fail to meet criteria for candidate drugs are generally not tested in successive models. Performing the model assays is no more than routine experimentation and consists of the same assay being repeated for each candidate compound.

Although pharmaceutical researchers design model systems to mimic the desired final target, it is true that occasionally compounds that show activity in lower models sometimes show less activity in higher models, including in humans. This is an accepted part of research. Situations where promising compounds are less active in lower models than in higher models are minimized by the selection of the appropriate model. Models which yield unacceptably high numbers of such compounds are discarded or re-designed.

The first paragraph of 35 U.S.C § 112 requires that the specification teach how to make and use the claimed invention. Applicants detail *in vitro* assays in which several of the claimed inhibitors were tested. Applicants further detail an *in vivo* model for testing the claimed inhibitors and set forth the results for one of the claimed compounds. Following these models, those skilled in the art would readily be able to make and use all claimed inhibitors.

Applicants attach hereto several references detailing the use of mouse models and correlation to human use in a model system similar to that of the present invention. Several of the attached references also describe the applicability of mouse models to the inhibition of osteoclastogenesis in humans.

Much of the molecular biology central to osteoclast biology was initially observed in mice. For example, the Shaloub *et al.* reference (British J. Haematology, 2000, 111, 501-512) discusses characterization of the cytokine osteoprotegrin (OPGL). Shaloub states that the binding of OPGL to receptors on mouse osteoclast precursors initiates osteoclasts differentiation. Shaloub further indicates that OPGL binding also occurs in human osteoclasts cells.

Bekker *et al.* (J. Bone Mineral Res., Vol. 16, No. 2, 348-60, 2001) indicates that the administration of OPG [a receptor for OPGL] to humans would result in a decrease in bone resorption" (Bekker *et al.*, p. 349) and describes the effects of a single dose of osteoprotegrin in postmenopausal women. As the molecular biology of osteoclasts biology in mice also applies to humans, the use of *in vivo* and *in vitro* mouse models is appropriate to predict which inhibitors will be active in humans.

There are many examples of mouse models used to measure inhibition of osteoclasts differentiation and function. Lacey *et al.* (Cell, 93(2):165-75, 1998) discusses a mouse bone resorption model. Li *et al.* (Proc Natl Acad Sci USA 97(4):1566-71) and Kong *et al.* (Nature, 397, 315-323, **1999**) discuss bone biology models using $RANK^{-/-}$ mice.

Mouse models of bone biology are clearly relevant and useful for predicting which inhibitors will be effective in larger animals including humans as the molecular biology of bone biology in mice is very similar to the bone biology in humans. Applicants direct the Examiner's attention to the Li *et al.* reference (Nature Genetics (1999) Vol. 23, 447-51) which discusses a putative osteoclast-specific proton pump subunit termed OC-116KD. Disruption of *ATP6i,* the gene for OC-116KD, resulted in severe osteopetrosis in mice. Although Li *et al.* do not report testing for the presence of OC-116KD in humans, the authors state that "[t]he osteoclast-specific expression of *ATP6i* and the bone-specific phenotype of *ATP6i* -/- mice suggest that *ATP6i* may be a useful target for therapeutic design and intervention in skeletal diseases manifesting with increased bone or cartilage resorption." (see page 450).

In Frattini *et al.*, (Nature Genetics 25, 343-6, 2000), the authors state that:

> autosomal recessive malignant osteopetrosis (arOP) has been mapped to 11q13, a region containing many potential genes for osteopetrosis. In mice, inactivation of one of the genes in this region, *Tcirg1*, encoding the osteoclast-specific 116kD subunit of the vacuolar proton pump causes osteoclast-rich osteopetrosis. In addition, a deletion involving the 5' portion of the gene underlies the spontaneous *oc/oc* mutation in mice.

(see page 343) Additionally, the authors report that mutations of *TCIRG1* are responsible for a subset of arOP in humans (see page 345). In Kornak *et al.*, (Cell, 2001, vol. 104:205-15), the authors discuss a chloride channel, CIC-7 found in both mice and men that is implicated in various forms of osteopetrosis. The authors state that the similarity of the "mouse model to the

human disease prompted us to search for mutations [of other genes] in 12 cases of infantile malignant osteopetrosis." (see page 210). Scimeca *et al.* (Bone 2000 Vol. 26, No. 3, 207-13) notes that the:

> gene conservation [in bone disease] between mice and humans has been very helpful in designing new probes to refne the physical map. Morevover, it has been a source of candidate genes for positional cloning in both species.

(see page 207).

The mouse model is clearly accepted by those skilled in the art as appropriate for predicting which inhibitors are likely to be effective in humans.

Applicants respectfully remind the Examiner that it is the mandate of the U.S. Patent and Trademark Office to ensure that patent applications comply with the requirements of the patent laws, in this instance to 35 U.S.C. §112. Determining which animal model is relevant to the testing of pharmaceuticals is **not** in the Patent Office's bailiwick. As set forth in MPEP §2107, questions of drug safety or effectiveness in humans is not a concern of the patent office. Such questions are routinely dealt with by the Food and Drug Administration. As discussed above, requiring the specific testing of the inhibitors encompassed by the present claims in order to satisfy the how-to-use requirement of §112 "would delay disclosure and frustrate, rather than further, the interests of the public."

Lastly, the Office Action, referring to Takasaki *et al.*, alleges that there are a number "of difficulties in applying the compounds at issue for human therapy", referring to issues including alleged "poor bioavailability and stability, expense, and risk of severe and occasionally life-compromising side effects" of large biomolecules (citing page 1266 of Takasaki). The Examiner also notes that Taksaki *et al.* supports a finding of unpredictability in determining which inhibitors would be active, stating that although Takasaki created 18 different peptides, "only one gives near wild type levels, and only three more give substantial inhibition." (Office Action at page 4). Applicants disagree with the Examiner's conclusions.

The Examiner is misconstruing Takaski. Although Takasaki does discuss small peptides, the passage cited by the Examiner describes large macromolecules "such as antibodies or TNF-receptor-Fc chimeras" which are significantly larger than the inhibitors

described and claimed in the present application. As to the Examiner's suggestion that because only 4 of the peptides dervied by Takaskia from the wild-type sequence showed inhibition the invention was unpredictable, Applicants assert that this hit-rate would satisfy the art-skilled. Indeed, as only routine experimentation is involved in running inhibitors in this model, the art-skilled would welcome the result that over 22% of the peptides showed activity. Takaski, instead of showing unpredictability, actually provides proof of concept and indicates that Applicants' invention is predictable.

The skilled artisan would not have to engage in undue experimentation to practice any desired embodiment of the subject matter encompassed by the pending claims because the specification provides detailed guidance as to make and use the claimed inhibitors. The *in vivo* and *in vitro* experiments described in the present application permit testing of the inhibitors presently claimed and are clearly appropriate for the human model. Applicants have thus enabled the skilled artisan to practice the subject matter defined by the present claims without undue experimentation, and accordingly respectfully request withdrawal of the rejection upon reconsideration.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-48 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Office Action alleges that the terms "inhibiting osteoclastogenesis", "an amount of an inhibitor effective to inhibit osteoclastogenesis", an amount of an inhibitor effective to inhibit such bone loss", "inhibiting bone resorption", and "an amount of an inhibitor effective to inhibit bone resorption" are indefinite. The Office Action alleged that it is not clear whether the inhibitor "inhibits all the symptoms or some of the symptoms, or inhibits for a short period of time or increases the survival of the patient . . . or cures the diseases." (Office Action at page 6). Applicants respectfully traverse this rejection.

The proper inquiry, when determining whether a claim satisfies the requirements of 35 U.S.C. §112, second paragraph, is a determination "whether those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics Inc. v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986).

Thus, if those skilled in the art can understand what is claimed when the claim is read in light of the specification, a rejection under 35 U.S.C. §112, second paragraph, is inappropriate.

The specification provides several definitions of the term "therapeutically effective amount." for example, on page 6, lines 12-19 of the application as filed, and on page 34, lines 20-26 which states:

> the compounds of the present invention, or pharmaceutical compositions thereof, are administered or applied in a therapeutically effective amount. By therapeutically effective amount is meant an amount which is effective to ameliorate, or prevent the symptoms of the disease or disorder, or prolong the survival of the patient being treated. Determination of a therapeutically effective amount is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure provided herein.

Additionally, the specification provides means of estimating a therapeutically effective dose based on the IC_{50} of a compound in an *in vitro* assay and allowing adjustment of the dose based on plasma levels, effective local concentration of the compound, and the specific status of the individual to whom the compounds are administered. (*See* page 34, line 27 to page 35, line 17 of the application as filed.)

The specification also provides definitions of the term "inhibit", for example, on page 6, lines 20-24 of the application as filed, which states that inhibit means "to decrease the amount, quality, or effect of a particular activity and is used interchangeably with the terms 'reduce', 'minimize', and 'lessen' . . . . ."

As set forth above, the "effective amount" of the compounds of the present invention ameliorates or prevents the symptoms of the disease or disorder or prolongs the patient's survival. Therefore, the inhibitor can inhibit all the symptoms **or** some of the symptoms, can inhibit the disease or disorder for a short period of time **or** cure the disease.

The Office Action further alleges that the use of two different symbols, " ≝ and "=" to define the same concept of covalent linkage renders the claims unclear. Applicants respectfully traverse this rejection.

One skilled in the art would readily understand the instant usage of the two different symbols, " ≝ and "=" to define the concept of covalent linkage. The two different symbols

were used to differentiate between linkages 1) between peptides and other peptides; and between peptides and "moieties having one functional group capable of forming a covalent linkage"; and 2) between "moieties having three functional groups capable of forming covalent linkages" and other "moieties having three functional groups capable of forming covalent linkages".

Applicants respectfully request the reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §102

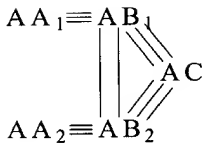
The standard for anticipation under §102(b) is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

Claims 1, 17, and 31-33 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Stahl *et al.* (U.S. Patent No. 5,470,952; "Stahl"). The Office Action alleges that Stahl discloses a method for inhibiting osteoclastogenesis, bone loss, and osteoporosis, and also for inhibiting bone resorption.

Claims 1, 17, and 31-33 have been cancelled without prejudice, rendering this rejection moot.

Claims 1, 17, and 31-34 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Yamaguchi *et al.* (J. Biol. Chem., 273(9), 5117-23, **1998**; "Yamaguchi"). The Office Action alleges that Yamaguchi teaches a method for inhibiting osteoclastogenesis and bone loss.

Claims 1, 17, and 31-33 have been cancelled without prejudice, rendering this rejection moot as it applies to those claims. Claim 34 recites, *inter alia*, that the inhibitor has the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of a TNF-R superfamily member, and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

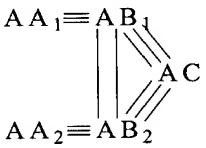
AB_1 is a moiety having a first functional group capable of forming a covalent linkage with one terminus of AC, a second functional group capable of forming a covalent linkage with AB_2 and a third functional group capable of forming a covalent linkage with AA_1;

AB_2 is a moiety having a first functional group capable of forming a covalent linkage with the second terminus of AC, a second functional group capable of forming a covalent linkage with AB_1 and a third functional group capable of forming a covalent linkage with AA_2;

AA_1 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_2;

AA_2 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_2.

In general structural terms, the inhibitor of claim 34 comprises a molecule having two internal sites, AB_1 and AB_2, wherein AB_1 and AB_2 are linked by an intramolecular covalent bond and by AC.



(I)

Yamaguchi *et al.* discusses the "Characterization of Structural Domains of Human Osteoclastogenesis Inhibitory Factor". As acknowledged by the Examiner, Yamaguchi discusses osteoclastogenesis inhibitory factor (OCIF) present "both as a ~60kDa monomer and a disulfide-linked homodimers." (Office Action at page 7). Neither the OCIF monomer nor the disulfide-linked homodimers teach or even suggest the subject matter of claim 34. The OCIF monomer is said to be approximately 60kDa and comprise about 401 amino acids. (Yamaguchi *et al.*, page 5117). However, the OCIF monomer is not described as being a molecule having two internal sites, AB_1 and AB_2, wherein AB_1 and AB_2 are linked by an intramolecular covalent bond and by AC. The "disulfide-linked homodimer" of Yamaguchi is said to have a disulfide bridge between Cys-400 of each monomer, which can be represented as follows.

$$\begin{array}{l} AA_1\text{-}AA_2\text{-}AA_3\text{-}AA_4\text{-}\,\text{-}\,\text{-}\,\text{-}\,\text{-}AA_{399}\text{-}\ Cys_{400}\text{-}\ AA_{401} \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \text{I} \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \text{I} \\ AA_1\text{-}AA_2\text{-}AA_3\text{-}AA_4\text{-}\,\text{-}\,\text{-}\,\text{-}\,\text{-}AA_{399}\text{-}\ Cys_{400}\text{-}\ AA_{401} \end{array}$$

The "disulfide-linked homodimer" of Yamaguchi fails to teach or even suggest a molecule having two internal sites, AB_1 and AB_2, wherein AB_1 and AB_2 are linked by an intramolecular covalent bond and by AC.

In view of the foregoing Applicants respectfully request the reconsideration and withdrawal of the rejection of claim 34 under 35 U.S.C. §102(b) in light of Yamaguchi *et al.*

Claims 8, 22, and 40 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Takasaki *et al.* (Nature Biotechnology, 15:1266-70, **1997**; "Takasaki"). The Office Action alleges that Takasaki discloses "peptides with different sequences including SEQ ID NO. 13, WP9QY, and also teaches the inhibitory activities of these peptides." (Office Action at page 7). Applicants respectfully traverse.

Claims 8, 22, and 40 are directed to methods for inhibiting osteoclastogenesis, methods for treating diseases characterized by bone loss, and methods for inhibiting bone

resorption, respectively, by administering an inhibitor of specific sequence. Takasaki, however, fails to teach or even suggest any method for inhibiting osteoclastogenesis, method for treating diseases characterized by bone loss, or method for inhibiting bone resorption, much less such a method using the specific sequences recited in claims 8, 22, and 40.

In view of the foregoing, Applicants respectfully request the reconsideration and withdrawal of the rejection of claim 34 under 35 U.S.C. §102(b) in light of Takasaki *et al.*

Claims 1-4, 9, 17-19, 23, 31-36, and 41 were rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Cheng *et al.* (U.S. Patent No. 5,849,865; "Cheng"). The Office Action alleges that Cheng discloses a method for inhibiting osteoclastogenesis, bone loss, and osteoporosis, "wherein the inhibitor comprises a peptide of a variety of number of amino acid residues which is bonded to different sequences and includes moieties with hydrophobic and hydrophilic characteristics." (Office Action at page 8). Applicants respectfully traverse.

Claims 1, 17, and 31-33 have been cancelled without prejudice, rendering this rejection moot as it applies to those claims.

Cheng *et al.* discusses "Peptides for Altering Bone Resorption, Angiogenesis and Restenosis" and recites that "the present invention provides Arg-Gly-Asp peptides that can alter the binding of osteoclasts to a matrix such as bone . . . " (*See* Abstract). Cheng *et al.*fails, however, to teach or even suggest the claimed invention.

Claims 2, 3, 4, 9, 18, 19, 23, and 34-36 each requires that element "AC is a peptide of 3-18 amino acid residues which corresponds in primary structure to a binding loop of a TNF-R superfamily member." Applicants were unable to find any reference to TNF in Cheng *et al*, much less to an inhibitor having a structure with AC being a "peptide of 3-18 amino acid residues which corresponds in primary structure to a binding loop of a TNF-R superfamily member." Similarly, Applicants were unable to locate any reference to any binding loop in Cheng *et al.*, much less to a TNF-R binding loop.

Although the Examiner specifically identifies SEQ ID NOS:26 and 27 as particularly relevant, Applicants note that Cheng *et al.* fails to identify either SEQ ID NO:26 or SEQ ID NO:27 as corresponding in primary structure to a binding loop of a TNF-R superfamily member.

As Cheng *et al*, fails to identify all the elements of claims 2, 3, 4, 9, 18, 19, 23, and 34-36, Applicants respectfully request the reconsideration and withdrawal of the rejection under 35 U.S.C. §102.

In view of the foregoing, Applicants respectfully request the reconsideration and withdrawal of the rejections under 35 U.S.C. §102.

Rejections under 35 U.S.C. §103

Claims 1-48 were rejected as being unpatentable under 35 U.S.C. §103 over Yamaguchi *et al.* in light of Greene *et al.* (WO 98/53842). Although the Office Action acknowledges that Yamaguchi fails to teach or suggest peptide inhibitors with 3-18, 1-6, 1-3, and 1-2 amino acids, the Office Action alleges that it would be obvious "to combine the TNF-R receptor-derived peptides and peptide analogues of Greene to make the claimed inhibitory peptides and use it to treat osteoclastogenesis." The Office Action further states that one of skill in the art:

> would have been motivated to make these inhibitory peptides to treat osteoclastogenesis, and would have expected reasonable level of success because Yamaguchi teaches that by analyzing the osteoclastogenesis inhibitory activity of deletion and C-terminal truncation mutants, he found that the N-terminal portion containing domains 1-4 is sufficient to inhibit osteoclastogenesis. Domains 1-4 correspond to the extracellular cysteine-rich regions of the TNFR family proteins.

(Office Action at page 10). Applicants respectfully traverse. As discussed above, Yamaguchi fails to teach or suggest the claimed invention.

As discussed above, Yamaguchi *et al.* fails to teach or suggest the claimed inhibitors. Instead of discussing small peptides, Yamaguchi identifies large peptides, most of which are over 300 amino acids in size. Although Yamaguchi does discuss making mutants of such large peptides, the smallest peptide disclosed appears to be about 197 amino acids in length (see mutant ΔD567 on page 5119 of Yamaguchi *et al.*). This peptide, although mutated, is still **significantly** larger than any of the claimed inhibitors. Yamaguchi fails to suggest modifying even the smallest disclosed peptide in such a way as to yield Applicants' claimed inhibitors.

Greene *et al.* fails to overcome the deficiencies of Yamaguchi *et al.* Greene does not teach or even suggest that the peptides disclosed are useful for inhibiting osteoclastogenesis,

instead stating that the compounds are useful for inhibiting diseases and disorders including cachexia, septic shock, autoimmune diseases, malaria, and lung fibrosis.

The Examiner has also failed to provide any motivation to combine the teachings of Yamaguchi with the teachings of Greene save the conclusory statement that domains 1-4 of Yamaguchi "correspond to the extracellular cysteine-rich regions of the TNFR family proteins." (Office Action at page 10).

"A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000). "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." *In re Dembiczak,* 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (quoting *Interconnect Planning Corp. v. Feil*, 774 F. 2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness, "there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). "In other words, the examiner must show reasons that the skilled artisan, confronted with he same problem as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1458 (Fed. Cir. 1998).

The Examiner has failed to provide such teaching, suggestion or motivation. If this motivation is based upon the Examiner's personal knowledge, Applicant requests that the Examiner provide an affidavit specifically reciting the knowledge of the Examiner that would provide the motivation to combine the cited references. 37 C.F.R. §1.104(d)(2).

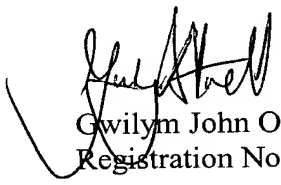
Applicants respectfully request the reconsideration and withdrawal of the rejections under 35 U.S.C. § 103.

Attached hereto is a marked-up version of the changes made to the application by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Conclusion

In view of the foregoing, Applicants respectfully urge that claims **2-16, 18-30, and 34-48** are in condition for allowance. A Notice of Allowance is earnestly solicited. Applicants respectfully invite the Examiner to contact the undersigned at (215) 564-8338 to discuss any issues unresolved by this response. A Notice of Allowance is earnestly solicited.

Respectfully submitted,



Gwilym John Owen Attwell
Registration No. 45,449

Date:
WOODCOCK WASHBURN KURTZ
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Attachments:
"Version with markings to show changes made"
Copies of references cited in Response

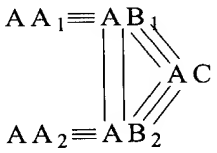
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please cancel claims **1, 17, and 31-33** without prejudice.

Please amend claims **2, 18, and 34** as follows.

Claim 2 (**Amended**) A method of inhibiting osteoclastogenesis comprising the step of administering to a patient an amount of an inhibitor effective to inhibit osteoclastogenesis, [The method of claim 1] wherein the inhibitor has the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of a TNF-R superfamily member, and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB_1 is a moiety having a first functional group capable of forming a covalent linkage with one terminus of AC, a second functional group capable of forming a covalent linkage with AB_2 and a third functional group capable of forming a covalent linkage with AA_1 ;

AB_2 is a moiety having a first functional group capable of forming a covalent linkage with the second terminus of AC, a second functional group capable of forming a covalent linkage with AB_1 and a third functional group capable of forming a covalent linkage with AA_2;

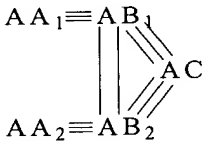
AA_1 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_2;

AA_2 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_2;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

Claim 18 **(Amended)** A method of treating patients who have diseases characterized by bone loss comprising the step of administering to said patient an amount of an inhibitor effective to inhibit such bone loss, [The method of claim 17] wherein said inhibitor is a compound having the formula:



(I)
wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of a TNF-R superfamily member, and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB_1 is a moiety having a first functional group capable of forming a covalent linkage with one terminus of AC, a second functional group capable of forming a covalent linkage with AB_2 and a third functional group capable of forming a covalent linkage with AA_1;

AB_2 is a moiety having a first functional group capable of forming a covalent linkage with the second terminus of AC, a second functional group capable of forming a covalent linkage with AB_1 and a third functional group capable of forming a covalent linkage with AA_2;

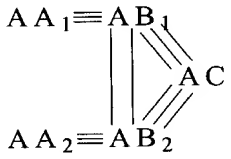
AA_1 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_1;

AA_2 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_2;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

Claim 34 (**Amended**) A method of inhibiting bone resorption comprising the step of administering to a patient an amount of an inhibitor effective to inhibit bone resorption, [The method of claim 33] wherein said inhibitor has the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of a TNF-R superfamily member, and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB_1 is a moiety having a first functional group capable of forming a covalent linkage with one terminus of AC, a second functional group capable of forming a covalent linkage with AB_2 and a third functional group capable of forming a covalent linkage with AA_1;

AB_2 is a moiety having a first functional group capable of forming a covalent linkage with the second terminus of AC, a second functional group capable of forming a covalent linkage with AB_1 and a third functional group capable of forming a covalent linkage with AA_2;

AA_1 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_2;

AA_2 is a moiety having hydrophobic properties and a functional group capable of forming a covalent linkage with the third functional group of AB_2;

"=" is a covalent linkage; and

"≡" is a covalent linkage.